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Oil Dispersants and Human Health Effects

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Introduction & Background

The explosion and subsequent blowout of the Deepwater Horizon (DWH) offshore drilling rig on April 20, 2010, led to the largest accidental offshore oil spill since the advent of the petroleum industry, dwarfed only by the deliberate release of crude oil by Iraqi forces during the Persian Gulf War. Over the time until the well was capped on July 15, approximately 200 million gallons of oil spilled into the Gulf of Mexico from the ocean floor beneath the well site located approximately 50 miles off the coast of Louisiana. For perspective, this amount is nearly 20 times the amount of oil discharged during the Exxon Valdez incident in Alaska. As a result, massive mitigation efforts took place during and after the flow of oil which entailed mechanical recovery, controlled burning, and chemical dispersion. As a result unprecedented application of oil dispersant agents was employed by BP during this time until their use was curtailed by the EPA on May 26, 2010. Overall, about 17 - 20% of the crude oil was mechanically recovered and 6 – 8% burned. For the oil remaining in the environment, about 40% (of original input) was evaporated, dissolved, or dispersed into small droplets by natural processes. Initially, it was estimated that only 16.5 million gallons of oil (<10% of total spill) were dispersed into the environment by chemical means, however this approximation was revised upward by 2-fold. The unaccounted for percentages of original oil presumably remain on the surface or washed on shore¹.

Oil dispersants are chemical mixtures of surface active agents and solvents designed to combine with large floating masses of oil and facilitate the dispersion of the oil into small microscopic droplets that then disperse throughout the water column. The micro-sized oil droplets can then be carried and diluted into the open ocean rather than wash ashore or adhere to wildlife and marine equipment. While it is assumed that dispersed oil is more readily degraded by microbial or physical processes, it can also increase the bioavailability of oil constituents and alter routes and extent of exposure to various toxic chemicals contained in the oil.

Potentially hazardous constituents of concern in dispersants

Currently there are 12 oil dispersant products approved for use by the US EPA and the chemical composition of most remains proprietary information. Even when the specific chemical ingredients are made available, the precise proportion of each entity contained in the product mixture is either not declared, or else specified only over a rather broad range. Table 1 lists these products along with their ingredients, if available. It is estimated that over 1.8 million gallons of

COREXIT 9500 and COREXIT 9527 were applied during these efforts, including the novel deepwater use of about 800,000 gallons injected below the ocean surface in an attempt to intercept the gushing oil plume located near the source. Early on in the mitigation effort COREXIT 9527 was used, however, due to limited on-hand availability, COREXIT 9500 was substituted as the primary product employed. It remains unclear as to how much of each particular product was used. As the crisis unfolded public perception and opinion became concerned with the additional threat to the environment and human health posed by application of hazardous chemicals in dispersants, as well as the toxic components within the oil itself. The initial withholding of information concerning the chemical composition of the dispersant contributed greatly to public concern. Identification of specific ingredients allows some estimation of their potential toxicity, however, it must be emphasized that human exposures to oil dispersants represent exposures to complex mixtures of the specific ingredients, as well as, in combination with oil components. Much less information is available regarding how such combinations of chemical agents might interact.

Broadly, the potentially hazardous effects represented by the oil dispersants can be divided into two classes. The first are direct toxic effects of the agents contained in the oil dispersant product. The second is the potential to modify the environmental deposition and/or bioavailability of toxic principals within the oil itself. This will be discussed in more detail below. It is difficult to comment on the specific ingredients contained in the products whose formulation remains a trade secret. We can, however, provide some insight regarding those whose formulation is known and, in fact, represent those used almost exclusively in the DWH incident (COREXIT 9500 and 9527). Therefore, we will restrict our discussion primarily to the following specific chemicals: Dioctyl sodium sulfosuccinate, 2-butoxyethanol, 1-(2-butoxy-1-methylethoxy)-2-propanol, and ethoxylated alcohols. Some of the products also contain various petroleum-derived products. For example, COREXIT 9500 contains a large amount (10 – 30%) of hydrotreated light petroleum distillate (CAS #64742-47-8), which contains primarily C₉ – C₁₂ saturated paraffinic hydrocarbons with less than 1% aromatic hydrocarbon content. Other distillate fractions employed as solvents may contain varying amounts of additional aliphatic and aromatic compounds depending on the distillation process. Numerous toxic effects, including malignancy, on a variety of target organs including central nervous system, lung, skin, liver, and bone marrow have been established for several of these components and thus they can contribute to the overall burden of toxic chemicals released during the DWH incident. Since, however, these chemicals are also present as components of the crude oil itself, we will limit our further discussion of toxicologic profiles to those agents specific to the dispersants. Sorbitan octanoate and its polyoxyethylene derivatives, used extensively as food and cosmetic additives, appear to be relatively non-toxic, aside from occasional reports of hypersensitivity and will not be discussed further. They may, however, like other surface active agents, contribute to the ability of dispersants to modulate exposure to oil components. We present here primarily toxicity data pertinent to single agents, however, it is important to remember that dispersants are complex mixtures and, thus, the potential for interactions between individual components is high, yet

difficult to predict.

Diethyl sodium sulfosuccinate (DSS) (IUPAC: Sodium 1,4-bis(2-ethylhexoxy)-1,4-dioxobutane-2-sulfonate) (CAS #577-11-7) is an anionic surfactant and a common ingredient in several household products. It is best known as the active ingredient contained in many over-the-counter stool softeners and laxatives (ex. Colace™, Ducosoft™, Ducolax™, Ex-lax™ stool softener among others). As such it is usually taken orally but can also be given by rectal enema. The recommended daily dose is between 50 and 200 mg (0.7 – 2.9 mg/kg b.w.) with up to 500 mg/day sometimes used. It also has been used as a pesticide on grapes, oranges, feed corn, almonds, nectarines². Systemic absorption after oral administration has been documented in humans³, but its extent has not been well studied. Absorption in the rat appears extensive with subsequent metabolism and combined urinary (60%) and biliary (40%) excretion. Some concern has been given regarding the potential to produce 2-ethyl-hexanol as a metabolite but so far this pathway appears to be nominal^{3b,4}.

Most of the untoward effects seem to be mechanism related and usually manifest as gastrointestinal symptoms including bloating, diarrhea, cramping, GI upset/pain. Prolonged use in the face of such symptoms can conceivably produce dehydration and electrolyte imbalances. The acute LD₅₀ in mice ranges from 1.5 g/kg⁵ to 4.8 g/kg⁶. The LD₅₀ in guinea pig was only 0.65 g/kg and horses appeared similarly susceptible to the adverse effects of the drug⁷. Cause of death was hypovolemic shock and circulatory collapse attendant with loss of fluid into the intestinal lumens, thus is essentially related to the mechanism of its therapeutic action. Several prolonged exposure studies similarly noted GI changes, however, consistently failed to show any changes in other systemic organ systems⁸. No evidence appears that DSS is carcinogenic. Chronic feeding of DSS (1% of diet) failed to show any promotional activity of tumors induced in response to 1,2-dimethylhydrazine (20 mg/kg/week, s.c) and, in fact, reduced the number of tumors seen at lower doses of initiator (10 mg/kg/week, s.c)⁹. In a three generation feeding study in rats 0.5 and 1% DSS in the diet caused a reduction in body weight, however, reproductive performance remained normal throughout the study and no treatment-related macroscopic changes were observed¹⁰. In a retrospective study where 6,937 women were prescribed drugs during the first trimester of pregnancy, 473 received DSS with only a single birth of a child with an unspecified congenital disorder¹¹. Allergic hypersensitivity reactions have been reported¹² but the incidence of anaphylaxis appears low. As reported by eHealthMe.com, a website that tracks post-marketing adverse event reporting to the FDA, only one case of anaphylaxis was reported out of the 411 people who reported side effects to Colace™¹³. Prescribing information for products containing DSS warn against concomitant use of mineral oil since therapeutic doses of DSS may enhance systemic absorption of mineral oil. This effect serves as a harbinger of the possible toxic interactions between oil dispersants and oil components.

2-Butoxyethanol (2-BE): 2-BE (CAS #111-76-2) (ethylene glycol monobutyl ether, monobutyl glycol ether, Butyl CelluSolve™, Dowanol™ EB) is a high-production volume solvent in the chemical class of glycol ethers. The structural formula of 2-BE is CH₃CH₃CH₂-O-CH₂CH₂-OH.

It is a member of a larger class of ethylene glycol ethers that include 2-methoxyethanol and 2-ethoxyethanol, as well as higher series of ethoxylated fatty alcohols. 2-BE is widely used in the manufacture of various enamels, lacquers, paints and other surface coatings. In addition, it is also commonly found in a variety of household cleaners and products. Because of its relatively high vapor pressure it can exist in the atmosphere as a vapor. 2-BE is also easily miscible in water and most organic solvents. Because of its aqueous miscibility, the propensity to produce a vapor phase is reduced upon addition to water. As such, the primary routes of exposure thought to be of concern are respiratory and dermal, although accidental/intentional ingestion of some 2-BE containing products have been documented. 2-BE can be readily absorbed via all three major routes of exposure. In fact, percutaneous absorption through the skin is thought to be a significant route of exposure for vaporous 2-BE within the atmosphere¹⁴. In addition, it appears that 2-BE is much more efficiently absorbed from an aqueous solution applied to the skin compared to an equivalent dose applied as a neat solution¹⁵. While most of the dispersant products are recommended for use as undiluted solutions for aerial application, others like COREXIT EC7664A, a surface washing agent, are applied as a 1- 3% diluted solution¹⁶. Boat spraying of COREXIT 9500 and 9527 products requires specialized low-pressure low-volume pumps, which if unavailable, may necessitate use of diluted product down to 5 – 10%.¹⁷

The metabolism of 2-BE proceeds mostly through typical alcohol and aldehyde dehydrogenase pathways with formation of 2-butoxyacetaldehyde and 2-butoxyacetic acid (2-BAA), the principal metabolite¹⁸. This raises the possibility of competitive inhibition of metabolism by other primary alcohols like ethanol and altered kinetics during consumption of alcohol. Administration of ethanol to rats significantly increased blood levels of various ethylene glycol ethers after their inhalation¹⁹. At higher concentrations this pathway is likely saturated and alternate pathways of O-dealkylation and glucuronidation become more quantitatively important^{18b}. An amino acid conjugate, n-butoxyacetylglutamine, has been identified in humans but not experimental animals²⁰.

The principal health effect of 2-BE observed in humans is central nervous system toxicity with additional kidney and liver injury at high doses. 2-BE can produce an acute CNS syndrome typical of exposure to other organic solvents consisting of dizziness, nausea, vomiting, loss of coordination, ataxia, confusion, depression, loss of consciousness. Severity is related to the dose. 2-BE is also an irritant to mucosal surfaces and skin, therefore ocular, oro-pharyngeal, nasal, respiratory, and dermal symptoms are also observed. 2-BE does not appear to be a skin sensitizer in humans²¹.

Acute LC_{50s} or LD_{50s} have been established in several species and are summarized in Table 2²². Much of the concern regarding 2-BE stems from its established ability to produce profound intravascular hemolytic anemia in experimental animals. This effect is characterized by a decreased number of circulating red blood cells (RBCs) and elevations in free hemoglobin. Free hemoglobin is believed to be responsible for the observed tissue damage especially in the kidneys and liver. Inhalation of 2-BE by female rats (62 ppm, 299 mg/m³) for 4 hrs increased

osmotic fragility of erythrocytes²³. This effect has been documented repeatedly in multiple species including dog, rabbit, and with both acute and longer term-exposure²³⁻²⁴. Older rats appear more sensitive than younger animals²⁵, as well as female compared to male rats²⁶. These observations likely reflect the greater accumulation of the metabolite 2-BAA in both sensitive groups (see below)^{25, 27}. In vitro studies using isolated erythrocytes have provided important insights into 2-BE induced hemolysis. The 2-BAA metabolite of 2-BE appears to be the primary offending species for these effects since in vitro incubation of isolated red blood cells with BAA produced hemolysis at between 20 – 40-fold lower concentrations than the parent compound^{24b, 28}. Importantly, the same studies observed marked species differences in sensitivity to the hemolytic effects. Human RBCs were markedly more resistant to these effects than rats^{24b, 28} requiring nearly 10 times more BAA to produce hemolysis. Other sensitive species include mice, hamsters, rabbits, and baboons, while resistant species include pigs, dogs, cats, and guinea pigs²⁹. These species differences in part reflect intrinsic differences in the red blood cells themselves, presumably at the level of membrane composition. 2-BE-induced frank hemolysis is rarely reported in humans, even during severe poisonings following suicide attempts (ingestion of 25 – 60 gm)³⁰. Occupationally relevant exposures (100 ppm) could produce headache and vomiting but no signs of hemolysis, although higher exposures have been shown to alter osmotic fragility when tested in vitro^{23, 31}. During a controlled human exposure study, vomiting and headache were observed after breathing 100 ppm (483 mg/mm³) for 8 hrs. No clinical signs of hemolysis were observed at any level although exposure to 195 ppm (942 mg/m³) did increase osmotic fragility of RBCs when assessed in vitro²³. After in vitro incubation of human RBCs with 2 mM BAA, a concentration which causes complete lysis rat RBCs, Udden observed no changes in morphology or deformability even in cells derived from patients with hereditary spherocytosis, a disorder characterized by red cells with high osmotic fragility, and sickle cell disease³².

Reproductive toxicity (both male and female) has been observed with the related glycol ethers, 2-methoxyethanol and 2-ethoxyethanol, however, 2-BE appears relatively devoid of reproductive and developmental effects. No testicular effects were observed in rodents exposed to 2-BE by inhalation of 800 ppm for 3 hrs³³ or oral administration of up to 2000 mg/kg/day, 5 days/week, for 5 weeks³⁴. Developmental studies exposing pregnant dams to 2-BE by a variety of routes failed to show any fetotoxic or teratogenic effects except at doses that produced significant maternal toxicity³⁵. While in vitro tests for mutagenic and genotoxic effects have yielded equivocal results³⁶ in vivo tests have been largely negative. 2-BE was negative in the bone marrow micronucleus test after i.p. administration in rats and mice^{36c, 37}. Using [³²P]-post-labelling assay, no DNA adducts were observed in multiple organs of orally dosed-rats³⁸. Keith et al. showed no effects on DNA methylation in multiple organs and tumor formation in FVB/N transgenic mice³⁸. 2-BE has been associated with formation of hemiangiosarcomas in liver and other organs of mice³⁹, however, these tumors are now thought to arise secondarily through the heme-dependent generation of reactive oxygen species and hypoxia-dependent proliferative signaling in endothelial cells, which arise during the hemolytic destruction of RBCs⁴⁰. Since

these tumors appear only in the context of profound hemolytic effects, they are thought not to be of significance in human exposures.

1-(2-butoxy-1-methylethoxy)-2-propanol (CAS # 29911-28-2), more commonly referred to as dipropylene glycol n-butyl ether (DPnB), is a component of both COREXIT 9500 and 9527. Synonyms for this compound include 2-(butoxypropoxy)-2-propanol, dipropylene glycol monobutyl ether, ARCOSOLV™ DPNB, or DOWANOL™ DPNB. DPnB is also a glycol ether, except it is classified as a P-series glycol ether (synthesized from propylene oxide) unlike 2-BE discussed above whose synthesis is based on ethylene oxide (E-series) as the starting material. In general, the P-series glycol ethers are frequently considered safer alternative to E-series compounds as they lack the hemolytic toxicity and appear to have less potential to disrupt reproductive function and fetal development⁴¹. Little of the descriptive toxicology, however, appears in the peer-reviewed literature but instead relies upon industry-sponsored unpublished studies. DPnB (Table 2), as well as other propylene glycol ethers, have very low acute toxicity with LD₅₀s greater than 1,800 mg/kg in oral studies, 2,000 mg/kg for dermal exposures, and >250 ppm for inhalation exposures⁴². In many cases, the actual LD₅₀ were not obtained within the dose range employed. When signs of toxicity were observed, they usually included generalized CNS and respiratory depression common with exposure to other solvents. DPnB was classified as "slight irritating" to skin and eyes⁴³, but no evidence of sensitization was observed⁴⁴. An intriguing peer-reviewed study, however, has recently appeared that begs further consideration. Choi et al.⁴⁵ conducted a case-control study correlating household levels of different classes of indoor air volatile organic compounds (VOCs) with allergic disease and IgE sensitization. Of the 8 different classes of VOCs including aromatic hydrocarbons, aldehydes, organic acids, and others, only the propylene glycol and glycol ethers were associated with increased risk of multiple allergic symptoms and atopy. Therefore, the association of glycol ethers to asthma and other allergic diseases deserves further attention although the actual offending chemical(s) have not been identified.

Longer term exposure studies also revealed relatively benign effects. Two-week inhalation studies in rats exposed to DPnB demonstrated a threshold for toxicity somewhere between 320 mg/m³ (40 ppm) and 810 mg/m³ (104 ppm)⁴⁶. Toxicity manifested primarily as histopathological lesions in the liver and nasal mucosa. In this regard, DPnB appears slightly more toxic than other propylene glycol ethers such as propylene glycol n-butyl ether⁴⁷. ^{47c}Dermal exposure to rats for up to 13 weeks produced some localized skin irritation at all doses but little in the way of systemic toxicity except small decreases in body weight and elevated neutrophil counts with a NOAEL of 0.1 ml/kg-day (91 mg/kg-day) and LOAEL of 0.3 ml/kg-day (273 mg/kg-day)⁴⁸. Prolonged oral exposure (13 weeks) produced slight elevations in liver and kidney weights without histopathology and mild changes in clinical chemistries only at the highest dose tested (1,000 mg/kg/day)⁴⁹. Importantly, these studies, as well as one specifically designed to test hematological effects⁵⁰, demonstrated that propylene glycol ethers do not share the hemolytic effects manifest by their E-series relative, 2-BE, as discussed above. Functional

reproductive studies with DPnB have not been carried out but no changes in the reproductive organs were observed at necropsy in any of the repeated dosing studies listed above and reproductive endpoints after exposure to the structurally-related propylene glycol monomethyl ether⁵¹ were negative. Developmental studies during dermal exposure of rats established a LOAEL of > 910 mg/kg/day (the highest doses applied in each study), respectively, for maternal toxicity, embryo-/fetal toxicity, or developmental aberrations⁵². In most studies DPnB is not mutagenic by in vitro or in vivo assays⁵³, however, three tests all from a single laboratory showed chromosomal aberrations in CHO cells⁵⁴. National Toxicology Program testing for carcinogenic effect of the related agent, propylene glycol monobutyl ether, observed an increase in hepatic tumors in male and female mice, but not rats exposed to 1,200 ppm by whole-body inhalation (the highest dose tested) for 2 years⁵⁵. Male mice showed exposure-related increases in non-neoplastic lesion in the kidney with equivocal increases in renal neoplasia. DPnB has not been similarly tested for tumorigenic potential in long-term studies. Therefore, with the paucity of in vivo data, as well as, equivocal in vitro results, formation of hepatic lesions with preneoplastic potential, and tumorigenic effects of structurally-related compounds, labeling DPnB as non-carcinogenic should be taken with some caution.

One likely explanation for the dramatic differences between the structurally similar 2-BE and PGBE relates to differences in metabolism. It is believed that the major offending species for hematologic and reproductive toxicity seen with the E-series glycol ethers is the corresponding acid produced during in vivo metabolism by alcohol and aldehyde dehydrogenases (2-butoxy acetic acid in the case of 2-BE). The major species (>95%) contained in commercial preparations of PGBE, however, is the alpha isomer which represents a secondary alcohol, thus is not a substrate for alcohol dehydrogenase and incapable of forming an alkoxypropionic acid. Instead, metabolism of PGBE proceeds largely by typical mixed function oxidase-dependent O-dealkylation yielding *t*-butanol and propylene glycol. Propylene glycol is readily converted to lactate and pyruvate for consumption in the Krebs cycle. *t*-butanol, as well as some of the parent compound, is excreted as a glucuronide conjugate⁵⁶.

Ethoxylated alcohols deserve a brief mention here in that they are chemically related to simpler glycol ethers. They are usually composed of a long chain fatty alcohol (C₈ – C₁₅) linked to a polyethylene glycol chain also of varying length (1-20). Modulation of the length of the carbon chains as well as the number of ethoxy units can be used to determine specific properties of these non-ionic surfactants. One of the approved oil dispersant products, DISPERSIT SPC 1000 contains ethoxylated alcohol specified as a mixture of C₁₂ – C₁₄ fatty alcohol without noting the relative degree of ethoxylation. While these chemicals have undergone considerable scrutiny in terms of their potential environmental toxicity, there is very little information regarding their effects on humans or other mammals. Various MSDS sheets for these compounds note them to be significant irritants upon ocular or dermal exposure, but no long term systemic toxicities are reported at typical usage exposures. One possible issue to consider is the fact that atmospheric (and perhaps microbial) oxidation of these chemicals can give rise to reactive aldehydes with

potential to produce contact sensitization and subsequent allergic reactions upon re-exposure⁵⁷.

Secondary effects by altering oil component exposure

Crude oil represents a complex mixture containing a vast array of aliphatic and aromatic hydrocarbons, heavy metals, and other substances. The total petroleum hydrocarbon (TPH) fraction represents the greatest concern to human health. Depending on the carbon chain length or number of aromatic rings each compound has its unique profile of volatility, solubility, and physical-chemical properties that ultimately determine its toxicokinetics and toxicodynamics. The low-molecular weight BTEX fraction (benzene, toluene, ethylbenzene, xylene) is of concern because they can diffuse into aqueous media as well as readily volatilize from a surface film of oil. The carcinogenic effects of benzene are well-known as a leading cause in acute myelogenous leukemia⁵⁸. Larger molecular weight species (naphthalene, benzopyrene) may remain more associated with the crude oil mass, but still possess toxic potential. An actual description of the specific adverse health effects of TPH is beyond the scope of this discussion, but the interested reader is referred to ATSDR profile for Total Petroleum Hydrocarbons⁵⁹.

Perhaps, the biggest question regarding the action of oil dispersants is how they might modulate the fate and transport of various oil constituents within the environment. By their nature they are designed to break up the oil mass into tiny micro-sized droplets that remain suspended within the water column rather than form a “slick” on the water surface. Wave tank experiments indicate the size of chemically-dispersed oil droplets to be in the 10 – 50 μm range with some even smaller, although the size of oil droplets formed over time after application of dispersants in the natural setting of an accidental spill is not well studied⁶⁰. This might reduce the evaporation of BTEX components, for example, reducing atmospheric concentrations and thus inhalational exposure. The concentration of these species, as well as heavier compounds, however, are now also increased within the water, and may promote exposure via dermal contact (swimming, water-on-skin exposure during clean-up operations, aerosol generation during wave action), as well as increasing the possibility that such chemicals might sequester in various marine biota because of their potential to bioaccumulate. Such physical dispersion of the oil mass into an emulsion of microscopically-sized particles dramatically increases the surface area of the overall oil-water interface where diffusion and absorptive processes proceed. The absence of a distinct odor of volatile oil components, as well as visual evidence of an oil slick could also impart a false sense of security when it comes to use of personal protection equipment such as respirators/filters, gloves, and other body coverings.

Of note is the hypothesis that the presence of oil dispersants can also directly affect how various chemicals enter the body. Again the increase in surface area whereby oil-derived chemicals might contact the skin and lung lining might facilitate absorption by the dermal and inhalation routes. We mentioned above that water mixtures of glycol ethers showed enhanced dermal absorption above that seen when glycol ethers are exposed neatly to the skin¹⁵, however, the dermal absorption of dispersed TPH components has not been compared to those in undispersed

oil. DSS, under the trade name Aerosol-OT, has received recent attention as a means to enhance oral absorption of various pharmaceuticals and is the subject of patents for improved drug-delivery systems⁶¹. DSS enhanced the efficacy of tetracycline on various microorganisms, including some normally resistant to the drug, by enhancing intracellular permeation of the drug⁶². Aerosol OT/1-butanol emulsions were also found to markedly enhance penetration of the antibiotic, clindamycin phosphate, through human epidermis when compared to a 70% isopropanol vehicle⁶³. The ability of Aerosol OT to similarly enhance diffusion of 5-fluorouracil through skin was accompanied by modifications in the lipid structure and degree of hydration of the stratum corneum layer of the skin⁶⁴. Thus, it is entirely possible that DSS and various other surface active agents in dispersant products can enhance absorption of specific TPH components and thus potentiate any adverse effects resulting from such exposures. Because of its volatility, most benzene applied to skin is expected to evaporate before substantial systemic absorption. If, however, benzene is sequestered into an emulsified aqueous suspension by the action of dispersants its potential for evaporation and, therefore, dermal absorption might be modified. While direct administration of DSS (1%) into the lungs of dogs produced some pulmonary edema⁶⁵, DSS aerosols (5%) accelerated lung clearance of the tracer, ⁹⁹Tc-diethylenetriamine pentaacetate (⁹⁹Tc-DPTA) without affecting gas exchange or lung mechanics⁶⁶. In fact, DSS has been considered as a means to enhance delivery of pharmaceutical agents via enhancing alveolar absorption⁶⁷. In rabbits, DSS successfully enhanced the absorption and biological action of insulin delivered by aerosol inhalation⁶⁸.

Probable exposure scenarios and possible at-risk groups

It is expected that those individuals directly involved with the clean-up operations and direct handling/application of the dispersants would have received the highest exposure and, therefore, are the most at risk for adverse effects. In these cases their most likely route of exposure was via inhalation or dermal absorption. The National Institute for Occupational Safety and Health conducted a limited series of health hazard evaluations for several groups of responders employed during the spill clean-up⁶⁹. The most commonly reported symptoms were headache, upper respiratory symptoms, and symptoms related to heat stress. While workers who reported exposures to oil and dispersants reported higher prevalence of all types of symptoms, no assignment of specific causative agents could be made. Health symptom surveys taken aboard two vessels actively engaged in releasing dispersants were similar in scope and magnitude to those obtained from other workers who had not worked on boats and had no exposures to oil or dispersants. Personal breathing zone and area air sampling was used to evaluate exposure to a variety of chemicals, including propylene glycol, a COREXIT component, and measured levels that were consistently below the acceptable occupational exposure limit (OEL). Moreover, NIOSH investigators consistently noted that workers generally complied with wearing the necessary personal protection equipment required for the task at hand.

Local populations residing on the shores are likely at minimal risk for toxicity based on dilution of the chemicals in surrounding water and air. Aerial application of dispersants occurred only at

distances greater than 3 miles from shore and serves to severely limit respiratory and dermal exposure on the shoreline. Some concern has been raised about potential contamination of seafood with chemical dispersants. The environmental half-life of these compounds is short and there is little evidence that any of the chemicals discussed above appreciably bioconcentrate or accumulate within the food chain. Trace levels of DSS measured in seafood samples tested after the opening of previously closed waters were considered insignificant to human health by the FDA.

As always the primary at-risk groups based on the limited knowledge we have are the very young, the elderly, and those with preexisting conditions especially chronic lung disease. The clean-up worker investigation conducted by NIOH noted a disproportionate number of smokers among the clean-up workers⁶⁹. Pregnant and nursing women should also be advised to minimize potential exposure simply as a matter of common sense. It is possible that the capacity for metabolism can also determine sensitivity. For example, individuals who possess high levels alcohol dehydrogenase activity (those of Asian or Amerindian descent, for example) might actually be sensitive to some of the effects of 2-BE compared to others with less functional capacity to generate the more toxic metabolite, 2-BAA. Similarly, genotypic/phenotypic variability in the cytochrome P450(s) responsible for O-dealkylation of propylene glycol ethers could contribute to alterations in the physiological disposition of P-series glycol ethers. No specific studies, however, have addressed these issues.

Perceived Safe Levels

No environmental or occupational regulatory/occupational standards for air or water exist for DSS. Because of its use as an OTC medicine and possible application of as food additive, the Acceptable Daily Intake as set by the WHO Joint Expert Committee on Food Additives is 6 mg/person/day and that set by the U.S. FDA is 30 mg/person/day. As a stool softener the recommended adult doses are in the range of 100 – 500 mg/day and appear to be well tolerated over extended periods of time. Because of their high vapor pressures, regulatory guidelines have been set for the glycol ethers. The following air standards for 2-BE have been set: TLV TWA (Threshold Limit Value, ACGIH) = 25 ppm, PEL (Permissible Exposure Limit, OSHA) = 50 ppm, and IDLH (Immediately Dangerous to Life or Health, NIOSH) = 700 ppm. No limits have been set specifically for DPnB, but those corresponding to dipropylene glycol monomethyl ether are TLV = 100 ppm and STEL (short-term exposure limit, ACGIH) = 150 ppm.

Potential relevant biomarkers and future studies

It will be a challenge to ascertain whether the application of oil dispersants into the Gulf of Mexico will have any perceptible effects on human health. The NIH-sponsored Gulf Long term Follow-up (GuLF) Study, led by NIEHS, is set to begin to study clean-up workers and volunteers to understand the scope and diversity of adverse health effects amongst those individuals most highly exposed to the toxic agents in question. One of its major challenges, however, will be to

accurately characterize and quantify exposure to specific oil and dispersant chemicals alone, as well as in mixtures. Clearly, one of the prime issues will be to determine specific populations who were exposed to these agents and quantify the extent of their exposure in terms of time and amount. Detailed clean-up worker histories might allow grouping of workers based on their proximity in time and space to actual application of dispersants and comparing their ultimate health outcomes to oil clean-up workers with similar tasks in regions where dispersants were not applied. Clearly, a more accurate way to document exposure (an internal dose) would be to measure parent compounds or their metabolites in biological samples (blood, urine, other). However, the pathways of metabolism of DSS are not well described. Measurement of urinary 2-BAA has proven useful in monitoring employees potentially exposed to 2-BE in other settings⁷⁰. It is important to remember, however, that these approaches are most useful only in the early stages following exposure since the compounds are presumably cleared fairly rapidly in the absence of a continuous exposure source. Moreover, there clearly are other sources of exposure for these agents such as laxative use and various household cleaning products containing glycol ethers. Therefore, for local residents not directly involved in clean-up activities, the background levels of exposure to many of these agents from other sources may approximate, or even exceed, those specifically from dispersant use. While biomarkers of effect would be useful, there are relatively few, if any, specific for these compounds. Measurement of RBC osmotic fragility could be used to monitor the hemolytic signature effect of E-series glycol ethers, but recall that humans are amongst the least sensitive species for this effect. Various measures of DNA damage and adduct formation in peripheral blood cells has provided some utility in measuring potential genotoxic effects after other oil spills.

The most fruitful future studies might be in regard to studying the interactions between oil dispersants and specific TPH components within the oil itself. Some chemicals in TPH might be more persistent than the dispersant chemicals so measurement of body burden with and without dispersant exposure might prove informative. Animal and in vitro studies that address availability and toxicity of TPH components in the presence and absence of dispersants should be carried out. For example, does simultaneous inclusion of dispersants in TPH component feeding studies alter the genotoxic and tumorigenic effects? Direct in vitro studies can easily be performed to determine if DSS or other oil dispersant components can increase permeation of oil components across skin. Human skin models employing cadaver-derived or tissue-engineered skin are routinely used to assess xenobiotic transport across this barrier in specifically-designed diffusion barrier chambers.

As pointed out earlier, the dispersant products themselves represent complex mixtures whose toxicity may not be adequately predicted by knowledge of the single ingredients alone. Few studies have directly tested the dispersant products for toxicity. Recently, the irritant and sensitizing properties of COREXIT 9500A and DSS were compared in a dermal application model in rats⁷¹. COREXIT was found to be about 10-fold more potent than would be expected based in its content of DSS alone. Acute 5 hr exposure of rats (27 mg/m³) of COREXIT aerosols

was found to induce a small change in lung compliance without inflammation⁷² and changes in peripheral vascular reactivity⁷³. These effects, however, were transient and extrapolation of the exposures conditions to those encountered in the real world is problematic.

Summary

The massive deployment of oil dispersants in the Gulf of Mexico in response to the DWH oil spill has raised concerns regarding their potential adverse effects to the environment and human health. The specific ingredients contained in many oil dispersant products remain proprietary information, however, those contained in COREXIT 9500 and COREXIT 9527, the products used almost exclusively in the Gulf, were available for review. Exposure of the general populace of Gulf shore to the major ingredients dioctyl sodium sulfosuccinate, 2-butoxyethanol, propylene glycol butyl ether, and other ethoxylated alcohols should be considerably below the range expected to produce adverse effects based on a review of their toxicological profiles. Of note, however, is the severe paucity of both human and laboratory data regarding the potential effects of chemical mixtures as represented by oil dispersant products. Those individuals involved in clean-up operations that directly handled oil dispersants or worked in the immediate area of application probably encountered greater amounts of dispersants and might a greater risk of adverse effects, but, in general these should be mild and self-limiting. Importantly, for several of the major toxicities described in experimental animals, humans appear to comparatively resistant. Perhaps a greater question pertains to the ability of dispersants to alter the toxicological properties of the chemicals contained in the oil itself. By their nature they are designed to alter the fate and transport of crude petroleum and its constituents and, therefore, can change the route and extent of human exposures. The physico-chemical properties of petroleum hydrocarbons contained in micro- sized oil droplets desperately needs to evaluated and compared to petroleum hydrocarbons alone, in simple aqueous solution, and in air. Moreover, some the oil dispersant products themselves have potential to directly modify biological barriers and, thus, alter permeation of oil-derived chemicals at various routes of exposure.

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Table 1. Approved Oil Dispersant Products and Their Ingredients

Product	Ingredients
BIODISPERS (Petrotech America)	Proprietary
JD-109 (GlobeMark Resources Ltd.)	Proprietary
JD-2000 (GlobeMark Resources Ltd.)	Proprietary
NOKOMIS 3-AA (Mar-Len Supply, Inc.)	Proprietary
NOKOMIS 3-F4 (Mar-Len Supply, Inc.)	Proprietary
COREXIT 9500 (Nalco Energy Services)	Sorbitan, mono-(9Z)-9-octadecenoate Sorbitan, mono-(9Z)-9-octadecenoate, poly(oxy-1,2-ethanediyl) <i>derivs.</i> Sorbitan, tri-(9Z)-9-octadecenoate, poly(oxy-1,2-ethanediyl) <i>derivs.</i> Butanedioic acid, sulfo-, 1,4-bis(2-ethylhexyl) ester, sodium salt (Diocetyl sodium sulfosuccinate) (10 – 30%) 1-(2-butoxy-1-methylethoxy)-2-propanol (1 – 5%) Distillates (petroleum), hydrotreated light (10 – 30%)
COREXIT 9527 (Nalco Energy Services)	Sorbitan, mono-(9Z)-9-octadecenoate Sorbitan, mono-(9Z)-9-octadecenoate, poly(oxy-1,2-ethanediyl) <i>derivs.</i> Sorbitan, tri-(9Z)-9-octadecenoate, poly(oxy-1,2-ethanediyl) <i>derivs.</i> Butanedioic acid, sulfo-, 1,4-bis(2-ethylhexyl) ester, sodium salt (Diocetyl sodium sulfosuccinate) (10 – 30%) 1-(2-butoxy-1-methylethoxy)-2-propanol (1 – 5%) Distillates (petroleum), hydrotreated light 2-Butoxy-ethanol (30 – 60%)
MARE CLEAN 200 (Taiho Industries Co. Ltd.)	Poly(oxy - 1,2 - ethanediyl), α - hydro - ω - hydroxy - , ether with 1,2,3 - propanetriol (9Z) - 9 - octadecenoate Poly(oxy - 1,2 - ethanediyl), α - (9Z)- 1 - oxo - 9 - octadecen - 1 - yl - ω - hydroxy- Poly(oxy - 1,2 - ethanediyl), α - (9Z) - 1 - oxo - 9 - octadecen - 1 - yl - ω - (9Z) - 1 - oxo - 9 - octadecen - 1 - yl oxy - (Polyethylene Glycol Dioleate) Sorbitan, tri-(9Z)-9-octadecenoate, poly(oxy-1,2-ethanediyl) <i>derivs.</i> (Polysorbate 85)

	Alkanes, C14-30
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Table 1. Approved Oil Dispersant Products and Their Ingredients (con't)

DISPERSIT SPC 1000 (U.S. Polychemical Corp.)	Poly(oxy - 1,2 - ethanediyl), α - (9Z)- 1 - oxo - 9 - octadecen - 1 - yl - ω - hydroxyl Ethoxylated Amines, tallow alkyl N,N-bis(hydroxyethyl)- Amides, coco Ethoxylated Alcohols, C₁₂₋₁₄-secondary, 1(or 2) - (2-methoxymethylethoxy) - propanol
SAF-RON Gold (Sustainable Environmental Technologies, Inc.)	Proprietary
NEOS AB3000 (Neos Company, Ltd.)	Proprietary
SEA BRAT 4 (Alabaster Corp.)	Proprietary

Table 2. Acute Toxicity of 2-Butoxyethanol (2-BE) and Dipropylene Glycol n-*t*-Butyl Ether (DPnB) in Various Species and Routes of Exposure

<u>Route of Administration</u>	<u>Species Tested</u>	<u>LC₅₀ or LD₅₀</u>
Inhalation		
2-BE	Male rats (4 hr) Female rats (4 hr) Mice (7 hrs) Guinea Pigs (1 hr)	486 ppm (2347 mg/m ³) 450 ppm (2174 mg/m ³) 700 ppm (3381 mg/m ³) 650ppm (3140 mg/m ³)
DPnB	Rats (4 hr) Rats (4 hr)	> 42 ppm (> 328 mg/m ³) (no deaths) > 262 ppm (> 2,040 mg/m ³) (no deaths)
Oral		
2-BE	Rats Mice Guinea Pigs Rabbits	2500 mg/kg b.w. 1400mg/kg b.w. 1200 mg/kg b.w. 320 mg/kg b.w.
DPnB	Rats Rats Mice	4000 mg/kg 1850 mg/kg 2160 mg/kg
Dermal		
2-BE	Rabbits Guinea Pigs	404-502 mg/kg b.w. 2000 mg/kg b.w.
DPnB	Rat	> 2000 mg/kg (no deaths)

(length of exposure)